REMARKS/ARGUMENTS

The Objections to the Specification Should Be Withdrawn

The specification has been objected to for not containing an abstract of the disclosure on a separate sheet as required by 37 C.F.R. §1.72(b).

The Examiner is respectfully reminded that the instant application is the U.S. National Stage of International Application PCT/EP2004/006069 and that the Office should have received from the International Bureau a copy of PCT/EP2004/006069 as filed, which includes the Abstract on a separate sheet. Therefore, Applicants believe that they should not be required to submit an additional Abstract on a separate sheet. However, as a courtesy to the Examiner, Applicants provide herewith the Abstract on a separate sheet (see, Appendix).

The specification has also been objected to for not reciting the continuity data. Applicants have amended the specification as suggested by the Examiner to include the continuity data.

The amendments to the specification are purely formal in nature and thus, do not introduce new matter.

In view of the amendments to the specification, the objections to the specification should be withdrawn.

Status of the claims

Claims 1-13, 18-20, 30-34, and 36 stand rejected, and claims 14-17, 21-29, 35, and 37 have been withdrawn.

Claims 3-11 and 20 have been cancelled without prejudice or disclaimer in the interest of expediting the prosecution of the instant application.

Claims 1, 2, 12, 13, 18, 19, 24, 33, and 36 have been amended.

Claims 1 and 2 have each been amended to be directed to a process for producing a of protein of interest in an F1 seed that involves the use of a replicating DNA comprising a geminiviral origin of replication and a nucleic acid sequence encoding a geminiviral replicase. These claims have been further amended to point out more distinctly that the claimed processes involve the active steps of hybridizing a first and a second transgenic parental plant, whereby an F1 seed is produced, and isolating from said Fl seed or a seedling thereof either the protein of interest or if said protein of interest is an enzyme, a chemical compound the synthesis of which said enzyme is involved in. Applicants have amended claims 1 and 2 in the interest of expediting prosecution of the instant application and not to limit the scope of their claimed invention. Support for the amendments to claims 1 and 2 can be found in original claims 1-11 and in the specification on page 7.

Dependent claims 12, 13, 18, and 19 have been amended to change dependency to claim 1 following the cancellation of claims 5 and 10. These amendments are formal in nature and thus, do not introduce new matter.

Claim 33 has been amended to replace the term "product" in line 1 with --protein-- to maintain antecedent basis following the amendment of claim 1 described above. The amendment of claim 1 also necessitated the deletion of the recitation of "said product of interest preferably being a protein of interest" from claim 33. The amendment of claim 33 is formal in nature and thus, does not introduce new matter.

Claim 36 has been amended to delete the recitation of "produced or" from claim line 1 interest of expediting prosecution of the instant application and not to limit the scope of their claimed invention.

Withdrawn claim 24 has been amended without prejudice or disclaimer to delete the recitation of the alternative "or RNA". This amendment was necessitated by amendment of

claim 1 to be limited to the use of replicating DNA. Claim 24 was further amended to change claim dependency from claim 5 to claim 1, due the cancellation of claim 5.

Applicants expressly reserve the right of file one or more continuing applications or take such other measures deemed necessary to protect the full scope of their invention as originally claimed.

No new matter has been added by way of the amendment of claims.

Claims 1, 2, 12-19, 21-37 are pending. Claims 14-17, 21-29, 35, and 37 are withdrawn. Claims 1, 2, 12, 13, 18, 19, 30-34, and 36 are under examination.

Reexamination and reconsideration of the application as amended are respectfully requested in view of the following remarks.

The Rejection of the Claims Under 35 U.S.C. § 112, Second Paragraph, Should Be Withdrawn

Claims 3, 20, 33, and 36 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regards as their invention. Claims 3 and 20 have been cancelled and therefore, the rejection of these claims is now moot. Claims 33 and 36 has been amended. This rejection with respect to claims 33 and 36 is respectfully traversed.

The Office Action indicates that the recitation of "preferably being a protein" in claim 33 fails to positively recite a required a claim element.

Due to the amendment of claim 1 described above, Applicants have amended claim 33 to omit the recitation "preferably being a protein". Accordingly, amended claim 33 is not indefinite.

The Office Action indicates that claim 36 is indefinite for the recitation of "produced or producible", alleging that his recitation is redundant. Although Applicants respectfully disagree that the recitation of the alternatives "produced" and "producible" renders claim 36 indefinite,

Applicants have amended claim 36 to delete the recitation "produced or". Accordingly, amended claim 36 is not indefinite.

In view of the amendments and the above remarks, it is submitted that the rejections of claims 33 and 36 under 35 U.S.C. § 112, second paragraph, should be withdrawn.

The Rejections of the Claims Under 35 U.S.C. § 112, First Paragraph, Should Be Withdrawn

Claims 1-3, 5-13, 18-20, 30-34, and 36 have been rejected under 35 U.S.C. § 112, first paragraph. Claims 3, 5-11 and 20 have been cancelled. Claims 1, 2, 12, 13, 18, 19, 33, and 36 have been amended. This rejection is respectfully traversed.

Written Description

Claims 1, 5-13, and 18-20 have been rejected under 35 U.S.C. § 112, first paragraph, for failing to comply with the written description requirement.

The Office Action acknowledges that the specification provides guidance for replicating DNA comprising a plant geminivirus origin of replication and a plant geminivirus replicase gene. The Office Action asserts, however, that the specification provides no guidance for replicating DNA from any other type of DNA virus, from any non-viral organism, from any non-plant virus, or from other geminiviral genes or sequences.

Although Applications respectfully disagree with this assertion of the Office Action, Applicants have amended claims 1 and 2 to be directed to the use of a replicating DNA comprising a geminiviral origin of replication and a nucleic acid sequence encoding a geminiviral replicase in the interest of expediting prosecution of the instant application. Accordingly, this rejection is overcome since the amended claims are directed to subject matter that the Office Action indicates is described by the specification.

In view of the amendment and remarks, it is submitted that the rejection of the claims under 35 U.S.C. § 112, first paragraph, for failure to comply with the written description requirement should be withdrawn.

Enablement

Claims 1-3, 5-13, 18-20, 30-34, and 36 have been rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement.

The Office Action indicates that the specification is enabling for a process for utilizing a replicating DNA comprising a plant geminivirus origin of replication and a plant geminivirus replicase gene, wherein the replicating DNA further comprises a divisible gene encoding a protein of interest, and wherein a functional protein product is isolated from transformed seeds comprising the rejoined portions of the protein-encoding gene. The Office Action asserts that the specification does not provide reasonable enablement for claims broadly drawn to the use of any non-exemplified replicating DNA from a multitude of sources, or for the production and isolation of non-exemplified functional products such as RNA or polymers.

Applications respectfully disagree with this assertion of the Office Action. However, without acquiescing to the position of the Office, Applicants have amended claims 1 and 2 to be directed to the use of a replicating DNA comprising a plant geminivirus origin of replication and a plant geminivirus replicase gene, wherein the replicating DNA further comprises a divisible gene encoding a protein of interest, and wherein a functional protein product is isolated from transformed seeds comprising the rejoined portions of the protein-encoding gene in the interest of expediting prosecution of the instant application. It is believed that the amended claims are fully enabled by the instant specification.

In view of the amendments and above remarks, it is apparent that those of skill in the art would be able to practice the present claims without undue experimentation. Accordingly, the enablement rejection of the claims should be withdrawn.

The Rejection of the Claims under 35 U.S.C. § 102 Should Be Withdrawn

Claims 1-4, 30, 31, 34, and 36 have been rejected under 35 U.S.C. § 102. Claims 3 and 4 have been cancelled. Claims 1, 2, and 36 have been amended. This rejection is respectfully traversed.

Claims 1-4, 31, 34, and 36 have been rejected under 35 U.S.C. § 102(e) as being anticipated by Szarka *et al.* (U.S. Patent No. 7,098,383). Claim 30 has also have been rejected under 35 U.S.C. § 102(e) as being anticipated by Szarka *et al.* (U.S. Patent No. 7,098,383) as evidenced by Sengupta-Gopalan *et al.* (*Proc. Nat. Acad. Sci. USA*, 1985, 82:3320-3324).

The Office Action indicates that Szarka *et al.* teaches the hybridization of parent plants containing either light or heavy chain encoding partial genetic endowments resulting in the production of F1 hybrid seeds that produce a multimeric immunoglobulin antibody. The Office Action does not indicate that Szarka *et al.* teaches a process for producing a protein of interest that involves replicating DNA. Furthermore, the Office Action does not indicate that Sengupta-Gopalan *et al.* provides evidence that Szarka *et al.* teaches such a process.

As discussed above, amended claims 1 and 2 are directed to processes for producing a protein of interest that involve replicating DNA. Szarka *et al.* fails to teach such a process. Accordingly, the claims are not anticipated by Szarka *et al.*

Claim 36 has been further rejected under 35 U.S.C. § 102(b) as being anticipated by each of Yadav (U.S. Patent No. 6,077,992) and EP 1 048 734 (SCRIPPS). The Office Action indicates that each of Yadav and SCRIPPS teach an F1 hybrid seed comprising recombined partial genetic complements sufficient for the production of a proteinaceous product of interest, wherein the seed was produced by hybridizing parent plants each containing a single partial genetic complement. The Office Action asserts that Yadav teaches a process for producing corn and soybean seeds which comprise a replicating DNA comprising a geminiviral origin of replication and a geminiviral replicase and a further comprising a gene encoding a desired proteinaceous product of interest.

As discussed above, claim 1 has been amended to be directed to a process that involves the production of seeds comprising a replicating DNA encoding a protein of interest and comprising a geminiviral origin of replication and a nucleic acid sequence encoding a geminiviral replicase. Claim 36 depends from claim 1.

In view of the amendment of claim 1, dependent claim 36 is novel over Yadav since Yadav does not disclose seeds comprising a replicating DNA encoding a protein of interest and comprising a geminiviral origin of replication and a nucleic acid sequence encoding a geminiviral replicase. In Yadav, a replication gene is provided in trans to the replicon. Furthermore, the seeds of Yadav or SCRIPPS are not producible according to the process of amended claim 1.

In view of the amendment of claim 1, dependent claim 36 is also novel over SCRIPPS since SCRIPPS does not disclose seeds comprising a replicating DNA encoding a protein of interest and comprising a geminiviral origin of replication and a nucleic acid sequence encoding a geminiviral replicase. Furthermore, the seeds of SCRIPPS are not producible according to the process of amended claim 1.

In view of the amendments and remarks, it is submitted that the rejection of the claims under 35 U.S.C. § 102 should be withdrawn.

The Rejection of the Claims under 35 U.S.C. § 103(a) Should Be Withdrawn

Claims 1-9, 13, 18-20, 30, 31, 33, 34, and 36 have been rejected under 35 U.S.C. § 103(a). Claims 3-9 and 20 have been cancelled. Claims 1, 2, 13, 18, 19, 33, and 36 have been amended. This rejection is respectfully traversed.

Claims 1-4, 30-31, 34, and 36 are rejected under 35 U.S.C. § 103(a) as being unpatentable over EP 1 048 734 (SCRIPPS) in view of Fiedler *et al.* (*Bio/Technology*, 1995, 13:1090-1093). The Office Action alleges that it would have been obvious to one of ordinary skill in the art to utilize the method of hybridizing parent plants for the production of a multimeric protein immunoglobulin protein of interest in F1 seeds as taught by SCRIPPS and to

modify this method by incorporating the seed-specific promoter and actual product isolation as taught by Fiedler *et al.*

Without acquiescing to any of the rejections under 35 U.S.C. § 103(a), Applicants have amended claims 1 and 2 in the interest of expediting prosecution of the instant application. As amended claims 1 and 2, are directed to the use of a replicating DNA comprising a plant geminivirus origin of replication and a plant geminivirus replicase gene, wherein the replicating DNA further comprises a divisible gene encoding a protein of interest, and wherein a functional protein product is isolated from transformed seeds comprising the rejoined portions of the protein-encoding gene.

In contrast to the teachings of SCRIPPS and Fiedler *et al.*, the present invention relates to the safe production of a protein of interest in hybrid seeds as stated in the on page 1 (lines 1-3) of Applicants' specification. Neither SCRIPPS nor Fiedler *et al.* relate to the problem of making a process for producing a protein of interest in seeds biological safe and better controlled. Therefore, one of ordinary skill in the art has no reason to consider either of these references alone or in combination with each other. Accordingly, Applicants' invention as presently claimed is not obvious in view of the combination of SCRIPPS and Fiedler *et al.*

Claims 1, 3-9, 13, 18-20, 30-31, 33-34, and 36 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Yadav (U.S. Patent No. 6,077,992). The Office Action alleges that it would have been obvious to one of ordinary skill in the art to utilize the method of producing high levels of proteins or other products of interest in F1 hybrid seeds as taught by Yadav and to modify that method by actually isolating the desired product from the seed using known protein isolation techniques.

Claims 10-12 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Yadav (U.S. Patent No. 6,077,992) as applied above to claims 1, 3-9, 13, 18-20, 30-31, 33-34, and 36 and further in view of Lyznik *et al.* (U.S. Patent No. 7,164,056). The Office Action alleges that it would have been obvious to one of ordinary skill in the art to utilize the geminivirus-mediated method of generating replicating DNA encoding a product of interest in F1 hybrid seeds as taught by Yadav and to modify that method by incorporating the recombinase/recombination

sequence for the generation of geminiviral replicating DNA encoding a proteinaceous product of interest as taught by Lyznik *et al.*

Yadav, whether considered alone or in combination with Lyznik *et al.*, fails to render obvious Applicants' claimed invention as explained in detail below.

Yadav mentions an expression system for a target gene, comprising:

(a) a chromosomally-integrated geminiviral proreplicon lacking a functional replication gene and comprising the target gene, and

(b) a chromosomally-integrated trans-acting geminiviral replication gene for the proreplicon.

The expression system of Yadav suffers from the disadvantage that replication genes for the viral proreplicon are widely present in nature. For example, a wild-type geminivirus occurring in nature can provide item (b) of the expression system of Yadav. Therefore, a wild-type geminivirus occurring in nature can infect a plant containing item (a), provide the geminiviral replication gene into cells of the plant and trigger expression of the target protein in a plant containing item (a) of the expression system of Yadav. Consequently, once item (a) is present in the environment, there is a high likelihood that item (b) also involved in the expression process is present in close spatial proximity, e.g. from a wild-type geminivirus. Therefore, distribution in the environment of the complete transgenic material for the expression system of Yadav occurs with high probability. The expression system of Yadav thus lacks biological safety, unlike Applicants' claimed invention.

Moreover, expression of the target protein is poorly controlled in the system of Yadav, since a wild-type geminivirus naturally present in the environment can trigger expression of the target protein at undesired points in time. A replication protein from a wild-type geminivirus will not be operably linked to a regulated or tissue-specific promoter, as taught by Yadav. Consequently, expression of the target protein may take place in various plant tissues infected by the wild-type virus. A plant containing item (a) of the system of Yadav cannot even be kept or transported uncontained without the risk that protein expression is triggered by a wild-type virus.

Therefore, the system of Yadav is not suitable for protein production in hybrid seeds in the open environment.

The process of amended claim 1 differs from Yadav *inter alia* in that Yadav does not disclose:

- a replicating DNA comprising a geminiviral origin of replication and a nucleic acid sequence encoding a geminiviral replicase,
- a second parental plant encoding a site-specific recombinase, integrase or flippase for generating said replicating DNA by rearranging the precursor of said replicating DNA by site-specific recombination,
- isolating, from said F1 seed or a seedling thereof, said protein of interest or, if said protein of interest is an enzyme, a chemical compound the synthesis of which said enzyme is involved in.

The process of amended claim 1 has the surprising advantage and unexpected result that biological safety and control over the production process of a protein of interest in hybrid seeds is fundamentally improved compared to Yadav. Applicants' invention provides for the first time a safe and reliable process for protein production in hybrid seeds suitable for use in the open environment.

In the present invention, site-specific recombination is used to rearrange the genome-integrated precursor of the replicating DNA for generating the replicating DNA. Site-specific recombination is specific for sites on the precursor of the replicating DNA. Site-specific recombinases, integrases or flippases specific for sites on the precursor of the replicating DNA are not widely distributed in nature as part of organisms or genetic material (such as plant viruses) that can easily infect a plant and provide a gene encoding such enzyme into cell nuclei of a plant. Importantly, plant viruses do in general not contain enzymes capable of site-specific recombination or genes coding for such enzymes. Therefore, the likelihood that a plant containing the first partial genetic endowment of the invention comes, in the environment,

unintentionally in contact with a site-specific recombinase, integrase or flippase under conditions where the site-specific recombinase, integrase or flippase can enter cell nuclei of plant cells is extremely low. Thus, both biological safety as well as control over the production process are high.

Yadav alone, or in combination with Lyznik *et al.*, does not render obvious the present invention for the following reasons.

1. Yadav does not relate to the problem of making a production process of a protein of interest in seeds biological safe and tightly controlled. Therefore, from Yadav, one of ordinary skill in the art has no reason for changing the expression system of Yadav so as to arrive at the present invention.

   The skilled person departing from Yadav has no reason to search for other documents in the field of plant biotechnology, since Yadav does not give an incentive for such search, nor does Yadav give an indication for a particular type of document in the field of plant biotechnology to search for. Importantly, Yadav does not contain an incentive for the skilled person to seek improvement of the system of Yadav in documents that relate to gene targeting such as Lyznik *et al.*

   2. Lyznik *et al.* relates to gene targeting, notably to solutions for increasing gene targeting frequencies. Therefore, the skilled person knowing Yadav has neither a reason to consider Lyznik *et al.*, nor a reason to expect an improvement of the system of Yadav from Lyznik *et al.* Since Lynik *et al.* does not relate to the problem of making a production process of a protein of interest in seeds biologically safe and controlled, the skilled person working on such problem has no reason to consider Lyznik *et al.*

3. There is no indication in Yadav nor in Lyznik *et al.* as to which of the many elements described in Lyznik *et al.* should be used to replace certain elements of the system of Yadav. Since the prior art is not aware of the unexpected improvement of the invention, this improvement was not available as a guidance

or selection rule for the skilled person before the present invention became known. The combination made by the Examiner required the hindsight knowledge of the present invention.

Claims 32-33 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Szarka *et al.* as applied above to claims 1-4, 30-31, 34, and 36 and further in view of WO 98/37211 (GENE SHEARS). The Office Action alleges that it would have been obvious to one of ordinary skill in the art to utilize the method of producing a protein of interest in an F1 seed obtained by hybridizing a first and a second transgenic plant as taught by Szarka *et al.* and to modify that method by incorporating male female sterile plants and/or female plants which comprise the genetic component necessary for the production of the protein of interest as taught by GENE SHEARS.

In contrast to the teachings of over Szarka *et al.* and GENE SHEARS, the present invention relates to the safe production of a protein of interest in hybrid seeds as stated in the on page 1 (lines 1-3) of Applicants' specification. Neither Szarka *et al.* nor GENE SHEARS relate to the problem of making a production process of a protein of interest in seeds biological safe and better controlled. Therefore, one of ordinary skill in the art has no reason to consider either of these references alone or in combination with each other. Accordingly, Applicants' invention as presently claimed is not obvious in view of the combination of Szarka *et al.* and GENE SHEARS.

In view of the amendments and remarks, it is submitted that the rejection of the claims under 35 U.S.C. § 103(a) should be withdrawn.

Request that Withdrawn Claims 24, 25, and 27-29 Be Examined in the Instant Application

Applicants respectfully request that the Examiner reconsider the restriction requirement and examine in the instant application withdrawn claims 24, 25, and 27-29 as limited to subject matter that is within the scope of amended claim 1. Because each of these withdrawn claims is dependent on amended claim 1, the subject matter of each of these withdrawn claims is within the scope of amended claim 1. Therefore, withdrawn claims 24, 25, and 27-29, like amended claim 1, are also directed to processes that involve a replicating DNA comprising a plant geminivirus origin of replication and a plant geminivirus replicase gene, wherein the replicating DNA further comprises a divisible gene encoding a protein of interest, and wherein a functional protein product is isolated from transformed seeds comprising the rejoined portions of the protein-encoding gene in the interest of expediting prosecution of the instant application. Applicants submit that the additional examination of claims 24, 25, and 27-29 would not constitute an undue burden on the Examiner, since no additional search would be required given that the subject matter of these withdrawn claims is within the scope of amended claim 1.

CONCLUSION

In view of the above amendments and remarks, Applicants submit that the rejections of the claims under 35 U.S.C. §§ 102, 103, and 112, first and second paragraphs, are overcome. Applicants respectfully submit that this application is now in condition for allowance. Early notice to this effect is solicited.

If in the opinion of the Examiner a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required

therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

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APPENDIX